Remarks

Claims 1, 5-8, 10-14, and 18-25 were pending, with claims 18-25 withdrawn. No claims are added or cancelled. Therefore, upon entry of this amendment, claims 1, 5-8, 10-14, and 18-25 remain pending, with claims 18-25 withdrawn.

Support for the claim amendment to claim 12 can be found throughout the specification, for example page 4, line 35 – page 5, line 1. Claim 5 is amended to remove a duplicate word.

No new matter is introduced by this amendment, nor the sequence listing.

Rejections under 35 U.S.C. §112, first paragraph: Enablement

Claims 1, 5-8, and 10-14 are rejected under 35 U.S.C. § 112, first paragraph on the ground that the specification does not reasonably provide enablement for using any antibody *in vivo* to induce apoptosis in any cancer cell. In particular, the Office states that "a generic claim embraces all species claims", and "[d]ependent Claims 12 and 13 require that the antibody induces apoptosis in a cell where the cell is a tumor cell. The claims encompass any kind of tumor cell occurring in vitro or in vivo in any mammal including a human." Applicants request reconsideration.

Claim 12 as amended now recites "a cell expressing the TRAIL receptor". Generic claim 1 relates to an antibody that recognizes a TRAIL receptor having a cytoplasmic death domain. The Examples of the present application demonstrate that the antibodies recognizing a TRAIL receptor of the present invention induce apoptosis in a cell expressing the TRAIL receptor (see, in particular, page 40, line 34 to page 42, line 20). Thus, the specification provides enablement for using the antibodies recognizing the TRAIL receptor, which are recited in claims 1, 5-8, and 10-14, to induce apoptosis in a cell expressing the TRAIL receptor.

In view of this amendment, Applicants request that the 35 U.S.C. § 112, first paragraph rejection be withdrawn.

Rejections under 35 U.S.C. §102

Claims 1, 5-8 and 10-14 are rejected under 35 U.S.C. § 102(b) as being anticipated Miller *et al.* (WO 01/77342). Applicants disagree and request reconsideration.

The Office maintains the rejection, stating the following (emphasis added).

Miller teaches on p. 42, lines 8-13:

> "The multivalent antibody may also comprise a polypeptide chain comprising the formula: (a) VL-CL- flexible linker- VL-CL- flexible linker- VL-CL; In this embodiment, the polypeptide may comprise three to about eight VL-CL polypeptides joined by flexlible linkers .... (c) (VL-CL), wherein n is three or more more (e.g. three to about eight, but preferably three or four); .... "
>
> Applicant's specification defines an Fv unit as a VH-VL where on p. 12 it states: "'Fv" is a dimer (VH-VL dimer) consisting of one unit of VH and one unit of VL bound very strongly by non-covalent bonding. The three complementarity determining regions (CDRs) of each variable region interact with each other, thereby forming an antigen binding site on the surface of the VH-VL dimer. Six CDRs confer an antigen binding site to the antibody."

As noted by the Office, the multivalent antibody of Miller *et al.* contains VL (L chain variable region) and CL (L chain constant region). In contrast, the antibody of claim 1 consists of at least one linker and at least three Fv units, which include VL and VH (H chain variable region). Thus the antibody of Miller *et al.* is clearly outside the scope of the claims of the present application. The claims are not anticipated by Miller *et al.* as they do not recite a CL region.

Therefore, Applicants request that the 35 U.S.C. § 102(b) rejection be withdrawn.

Objection to the sequence listing

Enclosed herewith is a new sequence listing. A "1" was added under "G" of "Gly" of SEQ ID NOs: 43 and 44.

In view of this submission, Applicants request that the objection to the sequence listing be withdrawn.

Rejection under 35 USC § 112, second paragraph

Claims 10 and 14 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants disagree and request reconsideration.

The Office asserts:

> a) Claim 10 is rejected because it is drawn to a limitation outside of the scope for the antibody recited in Claim 1. The antibody of claim 1 and dependent claims thereof is required to be at least a trimer or triabody, but dependent

Claim 10 requires two scFv molecules which is technically a dimer or diabody.

b) Claim 14 is rejected because it is drawn to a limitation outside of the scope for the antibody recited in Claim 1. The antibody of claim 1 and dependent claims thereof is required to be at least a trimer or triabody, but dependent Claim 14 requires a dimer (a tandem diabody) of an antibody with the amino acid sequence shown in SEQ ID NO: 8.

Claim 10 specifies that the antibody comprises two sc(Fv)2 molecules which have four Fv units (see page 13, line 35 to page 14, line 1 of the specification). Since claim 1 requires the antibody to have at least three Fv units, claim 10 is clearly within the scope of claim 1.

Claim 14 specifies that the antibody to comprise the amino acid sequence of SEQ ID NO: 2, 4, 6, or 8. SEQ ID NO: 2 (ScFvH2L), 4 (ScFvHIL), and 6 (ScFvHOL) are triabodies with three Fv units (see page 33,lines 13-16 of the specification). SEQ ID NO: 8 is a tandem diabody which has four Fv units (see page 15, lines 32-35). Since claim 1 requires the antibody to have at least three Fv units, claim 14 is clearly within the scope of claim 1.

Therefore, the 35 U.S.C. § 112, second paragraph rejection is improper, and Applicants request that it be withdrawn

If there are any minor issues to be resolved before a Notice of Allowance is granted, the examiner is invited to telephone the undersigned.

Respectfully submitted,

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